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Exercise improves learning and memory impairments in sleep deprived female rats

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HIGHLIGHTS

- Paradoxical sleep deprivation (PSD) impaired learning in ovariectomized female rats.
- PSD impaired short term memory in intact and ovariectomized female rats.
- Physical exercise alleviated the PSD-induced cognitive impairments in female rats.
- There was no significant change in the plasma corticosterone level of all groups.

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ABSTRACT

Inadequate sleep is a common problem in modern societies. It has been previously shown that female rats are more vulnerable to the deleterious effects of sleep deprivation on cognitive functions. Physical exercise has been suggested to attenuate the cognitive impairments induced by sleep deprivation in male rats. The objective of the current study was to investigate the effects of physical exercise on cognitive functions of female rats following paradoxical sleep deprivation.

Intact and ovariectomized (OVX) female Wistar rats were used in the present study. The exercise protocol was 4 weeks of treadmill running. The multiple platform method was applied for the induction of 72 h paradoxical sleep deprivation and the cognitive function was evaluated using Morris water maze (MWM). Plasma corticosterone level was evaluated in separate groups of study. ANOVA and repeated measures were used to analyze the data and $P < 0.05$ was considered statistically significant.

Throughout the investigation, significant learning impairment was observed in sleep-deprived OVX rats compared to the intact and the other OVX groups. Short term memory impairment was observed in both sleep-deprived OVX and intact groups. Physical exercise alleviated the PSD-induced learning and memory impairments in both intact and OVX groups. Corticosterone levels were not statistically significant among the different groups.

The results of our study confirmed the negative effects of PSD on cognitive functions in female rats and regular physical exercise seems to protect rats from these effects. Further studies are suggested to be carried out in order to evaluate the possible underlying mechanisms, and also to evaluate the possible interactions between sex hormones and PSD-induced cognitive impairments.

1. Introduction

Animal studies have demonstrated the positive effects of sleep on declarative and procedural memory in various behavioral tasks [1–4]. It has been shown that sleep contributes to the acquisition and consolidation of memory [4–6]. "Sleep" has been considered as a time window through which the acquired information is processed without any disturbance from the sensory system [2]. Sleep disorders are a common

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problem in modern societies affecting different aspects of individuals' lives and making alterations in the physiological function of both humans and animals [7,8]. Fragmented sleep and sleep deprivation, in the long period, can lead to mood changes, impaired mental ability, and disturbed performance [9–11]. It also has deleterious effects on the motor and the cognitive function [12]. Many animal studies have reported that PSD leads to impairments in hippocampus-dependent memory formation [13,14], emotional memory [15], working memory [16] and increased anxiety levels [17,18]. These pieces of evidence are partially explained based on the fact that the hippocampus is extremely vulnerable to sleep loss [14,19–21].

It seems that cognitive functions such as memory and learning [22,23] as well as different sleep aspects including its quality and pattern [24–26] are different in two genders. Changes in sleep patterns are often associated with hormonal factors — particularly estrogen level [27]. It is also noticeable that sex steroids are not only involved in the regulation of gonadal hormone secretions and reproductive behaviors, but also affect some functions such as one's cognitive performance and sleep pattern [28–30]. It has been previously shown that female rats are more susceptible to the deleterious effects of sleep deprivation on cognitive performance [31]. Female rats are also more vulnerable to stressful conditions [32].

Physical exercise has been shown to improve learning and memory in both MWM [33,34] and passive avoidance task [35] paradigms. Additionally, it has been observed that physical exercise also has multidimensional effects on brain performance, like enhancing angiogenesis [36] and neurogenesis [37,38] at the cellular level, increasing neuronal plasticity and upregulating the expression of BDNF mRNA in the hippocampus [39,40].

Exercise also plays a protective role against memory impairments observed in neurodegenerative diseases such as Alzheimer's disease [41,42]. Furthermore, it has been shown that exercise can improve memory functions during estrogen deprivation [43,44]. Previous studies have demonstrated the positive effects of physical exercise on memory impairments induced by sleep deprivation in male rats [45,46] while no study has been particularly devoted to female rats concerning this subject. Therefore, the objective of the current study was to evaluate the effects of physical exercise on the cognitive functions of sleep deprived intact and OVX female rats.

2. Material and methods

2.1. Animals

All experimental protocols and treatments were approved by the Ethics Committee of Kerman Neuroscience Research Center. We attempted to minimize the discomfort for the animals at all stages of the study (Ethics Code: KNRC-9-33). Female Wistar rats (3–4 months old, weighing 200–250 g) were used for the current study. Animals were caged in groups of four with ad libitum access to food and water. They were housed under controlled temperature (23 ± 1 °C) and 12-h light–dark cycle (lights on: 07:00–19:00 h).

Two sets of animals including intact and ovariectomized (OVX) were randomly allocated into the following subgroups: control (maintained in home cages), PSD, wide platform (Sham platform), naïve exercise, sham exercise and exercise + PSD. A sham surgery (sham ovariectomy) was also performed on a separate group of rats. All OVX and sham surgery (submitted to surgery without removing the ovaries) groups underwent ovariectomy surgical procedure (n = 8 for each group).

2.2. Surgical procedures

All surgical operations were performed under general anesthesia with a mixture of ketamine and xylazine (60 mg/kg, i.p. ketamine and 10 mg/kg, i.p. xylazine). Both ovaries were removed through a small mid-abdominal incision under aseptic conditions. After the operation, all rats were kept in the animal room for one month [43].

2.3. Exercise protocol

The rats in the exercise groups underwent forced exercise sessions (at 0° inclination) during the light cycle between 9:00 and 14:30, for four weeks, from Saturday to Wednesday (they received a mild shock (0.25 mA) whenever they stopped running). These rats were allowed to adapt to treadmill environment for 30 min during 2 consecutive days before the commencement of the exercise protocol, this was to eliminate the possible stress of the novel environment.

The exercise protocol was as follows: 30 min for the first two weeks (at a 10 m/min speed), 45 min for the third week and 60 min for the fourth week (both at 15 m/min speed). Every 15 min during each session, the animals were given a five minute break. Rats in the sham exercise groups were left on the treadmill, without running (0 m/min) for the same number of sessions and the same amount of time as those in the exercise groups [45].

2.4. Induction of paradoxical sleep deprivation (PSD)

A multiple platform apparatus was used for the induction of PSD. The apparatus (90 cm × 50 cm × 50 cm) contained 10 columns (10 cm high, 7 cm diameter located 2 cm above the surface of the water) which were arranged in two rows and spaced 10 cm apart (edge to edge), to allow rats to jump from one platform to another. In this paradigm, cage mates (4 rats) were placed together in the chamber to maintain social stability.

The rats had free access to clean water bottles, and food pellet baskets were always hanging from the top of the chamber. In the current study, PSD was induced for 72 h, as previously described [31]. PSD paradigm was carried out 24 h after the last exercise session in the exercise/PSD groups.

During the sleep deprivation period (72 h), the temperature (23 + 1 °C) and light/dark cycle were both maintained under controlled conditions.

We also tested the possible effects of novel environmental stress by placing the control rats in the similar chamber with wider platforms (sham platform) (10 cm high, and 15 cm in diameter), since it was large enough for the rats to sleep in without falling into the water.

2.5. Spatial learning and memory

As previously mentioned, MWM task was used to assay spatial learning and memory [31]. Rats became fully trained in approximately 3 h, as this was required to determine the effects of PSD on memory performance. In fact, the classic version of MWM (within 5 days of the training period) was not applicable for 72 h pre-training PSD.

The behavioral experiment was performed during the light cycle (between 8:30 and 12:00) 30 min after the PSD paradigm. The testing chamber was a black circular swimming pool which was painted with nontoxic materials (160 cm diameter, 80 cm high and 40 cm deep) and filled with water. Visual cues were placed around the chamber. The test chamber was divided into four equal quadrants. A square hidden black platform (10 cm diameter) was submerged beneath (1.5 cm) the water surface in the middle of the target quadrant in the pool. The sessions were recorded with a video camera located above the center of the pool and connected to a recording system (Noldus Ethovision® system, version 5, USA).

In the spatial acquisition phase, the rats were allowed to find a submerged hidden platform during a 60-second-interval in four training trials (inter-trial interval = 60 s) repeated in three blocks (inter-block interval = 30 min). After finding the platform, the animals were allowed to rest on the platform for 20–30 s.

The rats were dried with a towel and returned to their cages. After 20 to 30 s of rest, they were once again put in the chamber for the next trial. When a rat did not find the platform within 60 s, the experimenter would put it on the platform. On each trial, rats were randomly released into the water from one of the four quadrants of the maze with their faces toward the wall of the quadrant where they were released. Each rat had 4 different releasing points. Parameters such as latency and the traveled distance to find the platform were recorded in each trial.

Two hours after the acquisition phase, a probe test was performed to evaluate spatial memory retention. For the probe test, the platform was removed and each rat was allowed to swim for 60 s. The time and distance spent in the target quadrant (quadrant 4) were analyzed as a measure of spatial memory retention. Following the probe trial, rats had to complete a visible platform test to determine any possibility of PSD and exercise interference with sensory and motor coordination or motivation. In this test, the ability of animals to escape to a visible platform was evaluated (the platform was raised 2 cm above the water level and was visible with aluminum foil).

2.6. Plasma corticosterone measurement

In another set of experiments, the effect of exercise and PSD on corticosterone levels was evaluated in separate groups of animals ($n = 7$ per group) that underwent the same behavioral conditions except for MWM.

All procedures were conducted precisely between 8:10 and 8:30 AM (~10 min after the end of the PSD period). Animals were anesthetized with CO_2. Immediately after decapitation; trunk blood was collected in plastic polyethylene tubes on ice containing Na_2–EDTA as anticoagulant. The blood was centrifuged at 2600 rpm for 20 min at 4 °C. The plasma was collected into micro tubes and refrigerated at −80 °C in order to measure the corticosterone levels in all of the samples. Plasma samples were then analyzed by an ELISA kit which was usually used specifically for rats and mice by someone who was blind to the treatment of the animals.

2.7. Data analysis

The time and distance spent to find the hidden platform in the MWM training in the acquisition phase were analyzed using a two-way analysis of variance (ANOVA) along with repeated measures to determine the differences of the learning rates of the groups (group and block as the factors).

All of the collected data from the MWM probe trials, swim speed, and corticosterone levels were analyzed by a one-way analysis of variance (ANOVA). When statistical significance was found between groups, Tukey's post hoc multiple comparison test was performed to determine points of significant difference. The data were expressed as Means ± S.E.M., and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Spatial learning

During the acquisition phase, animals in all groups learned to find a hidden platform as observed by the reduction in their swimming distance and their escape latency across blocks of training (Figs. 1 and 2A, B). There was no significant difference in the distance and escape latency block trials in all of the intact female groups (Figs. 1 and 2A, respectively). Repeated measures analysis of ANOVA indicated that the distance and escape latency of PSD-OVX group significantly increased in block 2 ($P < 0.05$; see Figs. 1, 2B) and block 3 ($P < 0.05$; see Fig. 1B and $P < 0.01$; see Fig 2B, respectively) compared to the other OVX groups. In the MWM test the mean of the traveled distance (717.73 ± 57.02 vs. 437.56 ± 53.15; $P = 0.015$) and escape latency

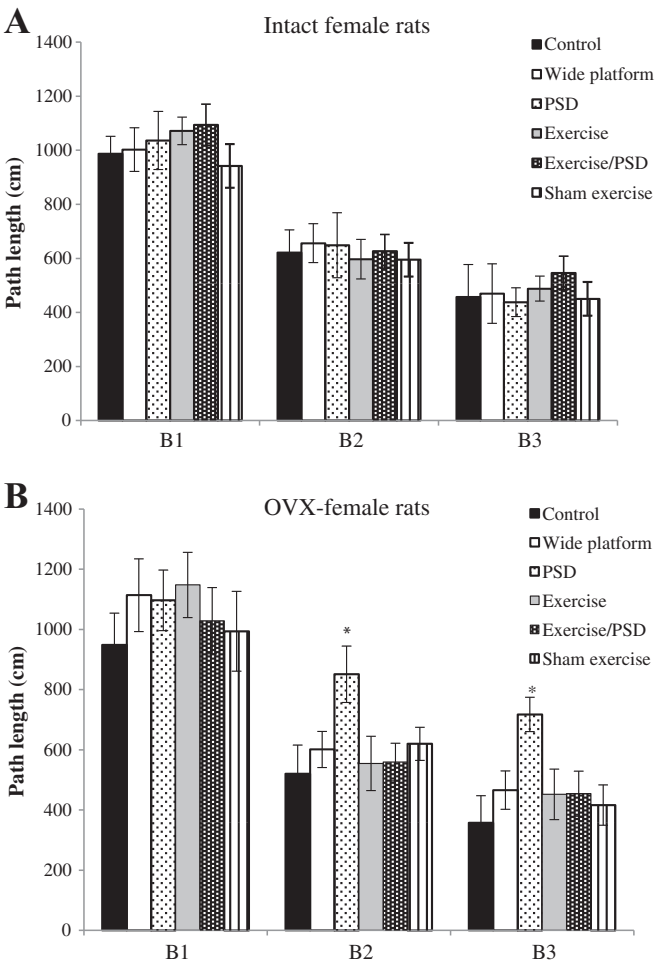

Fig. 1. The effects of paradoxical sleep deprivation (PSD) and exercise on the path length to reach the hidden platform in intact (A) and ovariectomized (OVX) (B) female rats in the Morris water maze test. All subgroups of intact female rats performed similarly during learning phase (A). Following 72 h PSD, the PSD-OVX group indicated an enhancement distance to reach the hidden platform than other groups, but regular treadmill exercise averted spatial learning impairment associated with PSD (B). There was no significant difference among the performance of the exercise, exercise/PSD, control, wide platform and sham exercise groups (A, B). Mean ± S.E.M. path length in hidden platform in 3 blocks had been calculated in all groups (8 rats/group). (*)$P < 0.05$, indicating the significant differences with other groups in blocks 2 and 3.

(33.61 ± 2.14 vs. 19.3 ± 2.4; $P = 0.005$) in block 3 also increased in the PSD-OVX group in comparison with the sleep deprived intact female rats. Meanwhile, the ability of the sleep deprived OVX rats to find the hidden platform was markedly improved through four weeks of treadmill exercise. This was also indicated by the significant reduction in their swimming distance (559.38 ± 62.64 and 454.47 ± 74.89 vs. 851.16 ± 93.76 and 717.73 ± 57.02; $P = 0.024$ and $P = 0.02$ in blocks 2 and 3 respectively; Fig 1B) and a reduction in the escape latencies (22.2 ± 2.59 and 19.37 ± 3.13 vs. 39.76 ± 5.56 and 33.61 ± 2.14; $P = 0.033$ and $P = 0.008$ in blocks 2 and 3 respectively; Fig 2B) in the MWM test (two-way ANOVA followed by Tukey's test and repeated measures analysis).

Among control, exercise, exercise/PSD, wide platform and sham exercise groups of intact and OVX female rats, the distance and escape latency to find the hidden platform in the water maze were not significantly different (Figs. 1 and 2A, B). Therefore, the exercise and exercise/sleep deprived groups of intact and OVX female rats did not perform significantly better than those of the control groups in their learning phase.

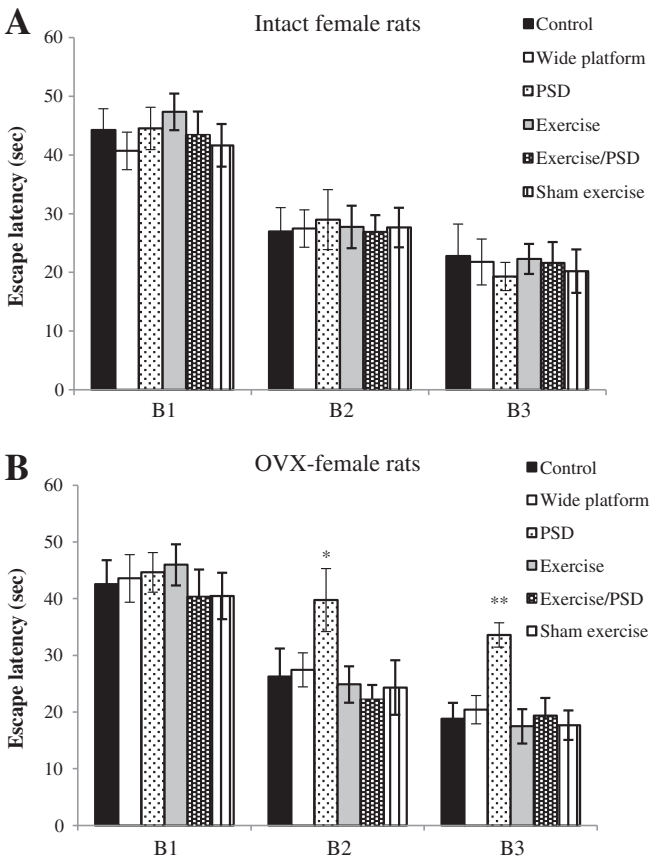

Fig. 2. The effects of 4 weeks of treadmill exercise and paradoxical sleep deprivation (PSD) on spatial learning in the Morris water maze test in the intact (A) and ovariectomized (OVX) (B) female rats. There was no significant difference in performance among all groups of intact female rats (A). Mean escape latency of PSD-OVX group increased significantly compared to the other groups. However, impairment in spatial learning caused by PSD in OVX female rats was reversed by regular treadmill exercise. (B). The exercise and exercise/sleep deprived rats did not perform significantly better than the control and sham groups (wide platform, sham exercise) (A, B). The accepted level of significance for the tests was $P < 0.05$. Data are expressed as mean ± S.E.M. ($n = 8$ rats). (*)$P < 0.05$ and (**)$P < 0.01$, indicating the differences with other groups in blocks 2 and 3 respectively.

3.2. Spatial short term memory

Two hours after the spatial learning phase, a probe test was conducted to examine short term spatial memory retention. The achieved results included the mean percentage (%) for time, distance and the number of crossing in the target quadrant.

The results of the probe test demonstrated that the sleep-deprived intact and OVX female rats spent less time and distance in the target quadrant compared to the control, wide platform, sham exercise, exercise and exercise/PSD groups (intact females: $P < 0.05$ for time and $P < 0.01$ for distance in the target quadrant; OVX females: $P < 0.001$ for time and distance in the target quadrant; Fig. 3A, B respectively), which indicated short term memory impairment. However, this impairment was prevented by 4 weeks of treadmill exercise in the exercise/sleep deprived groups since they spent more time and distance in the target quadrant than the sleep deprived rats (Fig. 3A, B). All of the intact and OVX female rats presented a similar number of crossing in the target quadrant in the MWM (Fig. 3A, B). There was no significant difference among the performance of the exercise, exercise/PSD, control, wide platform and sham exercise groups of intact and OVX female rats in the short term memory test (one-way ANOVA followed by Tukey's test).

Additionally, the sham surgery and control groups of intact and OVX female rats had similar performance in the MWM test (results not shown).

3.3. Latency to visible platform and swimming speed

In this study, the intact and OVX female rats had a similar escape latency and swimming speed in the MWM test ($P < 0.05$, Table 1). However, the regular treadmill exercise and PSD did not change the visible platform phase and the swimming speed, revealing no significant differences between the groups in visual and motor functions.

3.4. Plasma corticosterone levels

The one-way ANOVA analysis indicated no significant changes in the plasma corticosterone levels of all groups of the female rats ($P > 0.05$, Table 2).

4. Discussion

This study investigated the effect of four weeks of regular treadmill exercise on spatial learning and memory impairments induced by PSD in female rats. Our findings revealed that PSD alone impaired the spatial learning of the OVX rats. It also disrupted the short term spatial memory of both OVX and intact female rats. Animals that underwent regular physical exercise before PSD had an improved performance in MWM task compared to the sleep deprived animals. They also had a stronger memory as demonstrated in the probe test. The effect of regular exercise was prominent in OVX rats and exercise/PSD group showed a faster acquisition rate compared to the PSD group. Our behavioral assessment revealed that regular physical exercise had a counteracting effect on learning and memory impairments of the sleep deprived female rats.

Although several studies have indicated the contradictory effects of PSD and physical exercise on cognitive performance [45,47], the effect of physical exercise on PSD-induced memory impairments has not been fully investigated in female rats with respect to the role of female gonadal hormones.

Several studies have confirmed the important correlation between rapid eye movement (REM) and cognitive functions. PSD or REM sleep deprivation induces impairments in various types of learning and memory [16,19,21,48–52]. The male rats that underwent PSD demonstrated significant learning and memory impairments in different paradigms such as radial ram water maze [45,53], MWM [31,50] and also plus-maze discriminative avoidance task [49]. The effect of PSD on emotional memory in mice has also been previously established [15]. Furthermore, PSD decreases the ability to retain new information, and it disrupts memory consolidation [14,52,54]. It is believed that the negative effect of PSD on learning and memory is as a consequence of the deleterious changes in intracellular signaling molecules [45] and receptors, including NMDA [55] and AMPA receptors [16].

Based on our findings, it seems that removal of the ovaries resulted in an increased sensitivity of female rats to the negative effects of sleep loss on spatial learning compared to the intact female rats. Consistently, in another study, sleep deprived-OVX female rats had significantly more impaired learning ability in MWM test than sleep deprived-intact female animals [31].

It is also well documented that female sex steroid hormones have potential protective effects against a variety of neural insults, experimental brain injuries, and neurodegenerative diseases [54,56–58], though the possible underlying mechanism is not completely understood [58]. Some studies on humans reported that postmenopausal women are more susceptible to the deleterious effects of poor sleep on cognitive performances [26,59–61]. Additionally, another study demonstrated that estrogen replacement therapy has the advantageous effects on cognitive deficiencies attributed to sleep disturbances in postmenopausal women [62].

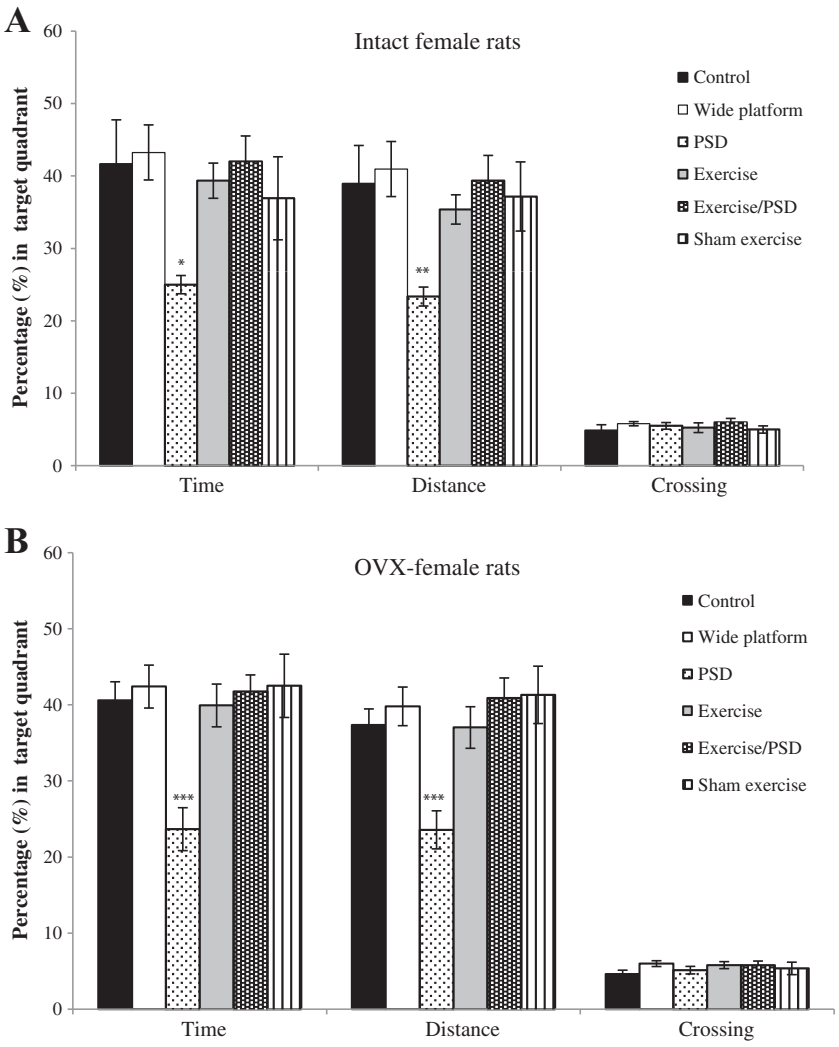

Fig. 3. The effects of regular treadmill exercise and paradoxical sleep deprivation (PSD) on spatial memory in the intact (A) and ovariectomized (OVX) (B) female rats. The time and distance in the target quadrant decreased significantly in the PSD intact and OVX female groups compared to the other groups. However, impairment in short-term memory caused by PSD in intact and OVX female rats was reversed by regular treadmill exercise. The number of crossing from the platform region was not significant in all groups. The probe test revealed no difference among the performance of the exercise, exercise/PSD, control, wide platform and sham exercise groups (A, B). Data are shown as mean ± S.E.M. (*)$P < 0.05$, (**)$P < 0.01$, (***) $P < 0.001$ indicating the significant differences with the other groups (8 rats/group).

Table 1
Swimming speed and latency to escape onto the visible platform in the intact and ovariectomized female rats.

	Swimming speed (cm/s)	Escape latency (s)
Intact		
Control	20.01 ± 3.75	15.51 ± 3.31
Wide platform	24.73 ± 2.26	13.41 ± 3.91
PSD[a]	25.15 ± 3.94	14.06 ± 1.12
Exercise	21.38 ± 2.99	12.93 ± 1.16
Exercise/PSD	24.82 ± 2.30	12.84 ± 3.36
Sham exercise	20.04 ± 3.58	12.23 ± 3.94
OVX[b]		
Control	21.63 ± 1.03	14.14 ± 4.14
Wide platform	20.33 ± 3.04	12.67 ± 4.27
PSD	22.81 ± 1.07	14 ± 3.55
Exercise	23.03 ± 1.59	13 ± 4.7
Exercise/PSD	23.89 ± 1.73	11.5 ± 3.28
Sham exercise	20.28 ± 3.7	15.14 ± 4.33
Sham surgery	20.05 ± 4.88	12.47 ± 1.75

Comparisons of swimming speed and latency to escape onto the visible platform in Morris water maze among groups were performed using one way analysis of variance (ANOVA) (the differences were not significant). Data are means ± S.E.M. (8 rats/group).
[a] Paradoxical sleep deprivation.
[b] Ovariectomized groups.

Table 2
Plasma corticosterone levels in the intact and ovariectomized female rats.

	Plasma corticosterone levels (pg/ml)
Intact	
Control	43.42 ± 4.98
Wide platform	49.85 ± 6.77
PSD[a]	47.57 ± 4.66
Exercise	51 ± 7.74
Exercise/PSD	52.28 ± 8.76
Sham exercise	41.5 ± 4.92
OVX[b]	
Control	37.71 ± 6.01
Wide platform	43.57 ± 5.16
PSD	38.14 ± 4.79
Exercise	37 ± 6.02
Exercise/PSD	42.86 ± 6.59
Sham exercise	38.28 ± 4.92
Sham surgery	39.86 ± 5.32

The one way analysis of variance (ANOVA) was used for the comparison of plasma corticosterone levels among the groups (the differences were not significant). Data are means ± S.E.M. (n = 7 per group).
[a] Paradoxical sleep deprivation.
[b] Ovariectomized groups.

Consistent with previous findings [31,45], our results indicated that rats which spent 72 h on the wide platforms did not differ much from the control rats in their spatial learning and memory ability. The outcomes of another investigation recommend that large platforms are not an adequate environmental control for multiple platform method. These may be a result of increasing stress in these procedures [63]. While another study has provided evidence that glucocorticoids do not play a role in cognitive deficits observed in sleep deprived rats [64]. Therefore, social stability in paradoxical sleep deprived rats (in multiple platform method) attenuates the levels of stress hormones compared to socially unstable groups [65]. There was no significant difference in plasma corticosterone levels among all groups of the female rats. Therefore, it is reasonable to conclude that the cognitive impairments observed in sleep deprived rats were due to the alterations in their sleep cycle and these impairments were not due to non-specific effects such as hypothalamic–pituitary–adrenal stress response (plasma corticosterone levels).

Several studies have analyzed the relationship between sleep deprivation and anxiety in animal models; although, the results have been controversial. Some studies reported an anxiogenic effect [17,18] while others reported that sleep deprivation did not change the anxious behavior and did not show elevated corticosterone level [31,66]. Furthermore, it was previously shown that regular treadmill exercise could normalize serum corticosterone level and decrease anxious behaviors induced by PSD in male rats [17]. Moderate exercise has been reported to produce antidepressant and anxiolytic behavioral effects in mice [67] and decreases the corticosterone level [37].

Additionally, an almost equal swimming speed and latency to reach visible platform in the experimental groups indicated that the observed changes were not due to the motor and visual impairments in the paradoxical sleep deprived rats.

Physical exercise is known to have positive effects on cognitive function. Zagaar et al. have demonstrated that regular treadmill exercise reverses PSD-induced impairments in short term memory and early long term potentiation (E-LTP) [45]. It has the same effects on long term memory and late LTP (L-LTP) in male rats [47]. These findings suggest that the protective effects of regular physical exercise on PSD-induced E-LTP and L-LTP impairments may be involved in increasing the BDNF level and other signaling molecules in the hippocampus [45,46]. Furthermore, the increase in BDNF protein level is particularly associated with cognitive improvement [39,40].

Although in this study we did not evaluate the underlying mechanisms, we suggest that alterations in LTP, expression of BDNF and other signaling molecules during physical exercise may be the possible underlying mechanisms leading to the positive effects of physical exercise on the impairments following PSD. Further studies are required to evaluate the exact mechanisms.

Although physical exercise seems to prevent cognitive impairment in the paradoxical sleep deprived rats, we did not observe any effect of treadmill running on spatial learning and memory in the intact and OVX control rats, which is consistent with the results of other studies [45,47]. However, some studies have shown that both voluntary and forced exercises improve cognitive function and facilitate acquisition and retention in various hippocampus-dependent tasks in normal subject [33,38,68–70]. Previously, it has been revealed that voluntary exercise can increase the cell proliferation in the hippocampus under estrogen-deprived conditions in female mice [44]. Another study reported that ovariectomy in rats caused the impairments of spatial navigation and aversive memory, and these cognitive effects were prevented by treadmill running exercise [43]. These conflicting findings may be due to the differences in the length, type and intensity of the exercise training used. Apart from these aspects, such different outcomes might be due to the differences in age and strain of the experimented animals.

It has been shown that regular physical activity has neuroprotective effects on cognitive decline associated with aging [71]. Regular physical activities can also improve cognitive performance in neurodegenerative diseases such as Alzheimer's disease [42,72] and brain ischemia [73].

In the current study, no significant difference was observed in learning and memory between the control groups of intact and OVX female rats. Therefore, estrogen deprivation over 30 days had no obvious effect on learning and memory in the MWM test. Other studies have demonstrated that changes in estrogen levels within more than 21 days have no significant effect on cell proliferation in the hippocampus [44,74]. Based on these investigations, although the specific mechanism is not yet obvious, the effects of estrogen deprivation on hippocampus functions may be temporary, and the hippocampus is likely to become accustomed to long-term estrogen deprivation.

In conclusion, the findings of this study demonstrated that regular treadmill exercise attenuated PSD-induced impairments of spatial learning and memory in the female rats. The results implied that exercise is likely to offer protection against PSD-induced impairments in learning and memory ability and hippocampus functions, especially in the OVX female rats.

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